TENT COOPERATION TRE. /

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 September 2000 (06.09.00)	
International application No. PCT/GB00/00260	**Applicant's or agent's file reference** PHM 70471/WO
International filing date (day/month/year) 31 January 2000 (31.01.00)	**Priority date** (day/month/year) 05 February 1999 (05.02.99)
Applicant FAULL, Alan, Wellington et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 August 2000 (21.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

Copy for the designated Office (DO/US)

PCT/GB00 00260

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield Cheshire SK10 4T
ROYAUME-UNI

Date of mailing (day/month/year)
10 August 2000 (10.08.00)

Applicant's or agent's file reference
PHM 70471/WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/00260

International filing date (day/month/year)
31 January 2000 (31.01.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
BRYANT, Tracey
Global Intellectual Property,
Patents
AstraZeneca UK Limited
Mereside, Alderley Park
Macclesfield Cheshire SK10 4TG
United Kingdom

State of Nationality:

State of Residence:

Telephone No.
01625 513 228

Facsimile No.
01625 583 358

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield Cheshire SK10 4T
United Kingdom

State of Nationality:

State of Residence:

Telephone No.
01625 513 228

Facsimile No.
01625 583 358

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[illegible]

[illegible]

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

[illegible]

' ⁻ENT COOPERATION TRE. '

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield Cheshire SK10 4T
ROYAUME-UNI

Date of mailing (day/month/year) 10 August 2000 (10.08.00)	
Applicant's or agent's file reference PHM 70471/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/00260	**International filing date** (day/month/year) 31 January 2000 (31.01.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ASTRAZENECA UK LIMITED 15 Stanhope Gate London W1Y 6LN United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address	State of Nationality	State of Residence
ASTRAZENECA AB S-151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] [illegible] [X] [illegible]

[illegible]
34, chemin des Colombettes
1211 Geneva 20, Switzerland

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 209/42, 409/14, 403/12, 401/12, A61K 31/40 — A1

(11) International Publication Number: **WO 00/46195**

(43) International Publication Date: 10 August 2000 (10.08.00)

(21) International Application Number: PCT/GB00/00260

(22) International Filing Date: 31 January 2000 (31.01.00)

(30) Priority Data:
9902459.8 5 February 1999 (05.02.99) GB

(71) Applicant *(for all designated States except US)*: ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: FAULL, Alan, Wellington [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). KETTLE, Jason [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

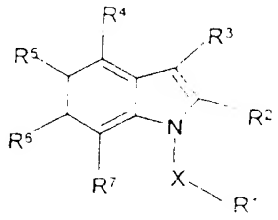
(74) Agent: BRYANT, Tracey; Global Intellectual Property, Patents, AstraZeneca UK Limited, Mereside, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: ANTI-INFLAMMATORY INDOLE DERIVATIVES



(I)

(57) Abstract

Therapeutic compounds of formula I wherein X is CH_2 or SO_2, R^1 is an optionally substituted aryl or heteroaryl ring, R^2 and R^3 are each independently groups R^{15} selected from $NHCOR^{15}$, $NHSO_2R^{15}$ or $OCONR^{16}R^{17}$ where R^{15} is optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl and R^{16} and R^{17} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, with the proviso that at least one of R^{16} or R^{17} is other than hydrogen, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms, and R^4, R^5 and R^6 are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl group or optionally substituted heterocyclic groups, and further provided that when R^4 is a group $NHCOR^{15}$, R^{15} is other than optionally substituted alkyl or optionally substituted heterocyclyl, and pharmaceutical compositions containing them are [illegible]

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 00/00260

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42 C07D409/14 C07D403/12 C07D401/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where ctical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 288 743 A (BROOKS ET. AL.) 22 February 1994 (1994-02-22) column 2, line 16 - line 21; claims; examples ---	1-10
A	WO 93 12780 A (MERRELL DOW PHARMACEUTICALS) 8 July 1993 (1993-07-08) cited in the application claims; examples ---	1-10
P,Y	WO 99 07351 A (ZENECA) 18 February 1999 (1999-02-18) cited in the application page 18, line 17 -page 19, line 7; claims; examples --- -/--	1-10

[X] [illegible] documents are listed in the continuation of box

[X] Patent family members are listed in annex

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" [illegible]

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" [illegible]

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/GB 00/00260

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 99 07678 A (ZENECA) 18 February 1999 (1999-02-18) cited in the application page 17, line 8 - line 17; claims; examples	1-10
P,X	WO 99 33800 A (HOECHST) 8 July 1999 (1999-07-08) claims	1,7

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 00/00260

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5288743 A	22-02-1994	MX 9307185 A	31-08-1994
		WO 9412179 A	09-06-1994
WO 9312780 A	08-07-1993	US 5318985 A	07-06-1994
		AT 185969 T	15-11-1999
		AU 3150993 A	28-07-1993
		CA 2124799 A	08-07-1993
		DE 69230224 D	02-12-1999
		DE 69230224 T	13-04-2000
		EP 0617616 A	05-10-1994
		JP 7504890 T	01-06-1995
		NZ 246114 A	26-10-1995
		US 5489579 A	06-02-1996
WO 9907351 A	18-02-1999	AU 8638198 A	01-03-1999
		NO 20000573 A	04-02-2000
WO 9907678 A	18-02-1999	AU 8638098 A	01-03-1999
WO 9933800 A	08-07-1999	AU 2052899 A	19-07-1999

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PHM 70471/WO

Box No. I TITLE OF INVENTION

CHEMICAL COMPOUNDS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ZENECA Limited
15 Stanhope Gate
LONDON
W1Y 6LN
GB

☐ This person is also inventor

Telephone No.
01625 515680

Facsimile No.
01625 583358

Teleprinter No.
669095/669388 ZENPHA G

State *(that is, country)* of nationality:
GB

State *(that is, country)* of residence:
GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FAULL, Alan Wellington
Alderley Park
Macclesfield
Cheshire
SK10 4TG
GB

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check box is marked, do not fill in below)*

State *(that is, country)* of nationality:
GB

State *(that is, country)* of residence:
GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicant and/or further inventor: see continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address:

Continuation of Box No. III **FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KETTLE, Jason
Alderley Park
Macclesfield
Cheshire
SK10 4TG
GB

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:

☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:

☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:

☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only *(If this check box is marked, do not fill in below.)*

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*.

- [X] AL Albania .....
- [X] AM Armenia .....
- [X] AT Austria .....
- [X] AU Australia .....
- [X] AZ Azerbaijan
- [X] BA Bosnia and Herzegovina .....
- [X] BB Barbados
- [X] BG Bulgaria .....
- [X] BR Brazil .....
- [X] BY Belarus .....
- [X] CA Canada
- [X] CH and LI Switzerland and Liechtenstein
- [X] CN China .....
- [X] CU Cuba .....
- [X] CZ Czech Republic .....
- [X] DE Germany .....
- [X] DK Denmark .....
- [X] EE Estonia .....
- [X] ES Spain .....
- [X] FI Finland .....
- [X] GB United Kingdom
- [X] GD Grenada
- [X] GE Georgia
- [X] GH Ghana .....
- [X] GM Gambia
- [X] HR Croatia .....
- [X] HU Hungary .....
- [X] ID Indonesia
- [X] IL Israel .....
- [X] IN India .....
- [X] IS Iceland
- [X] JP Japan .....
- [X] KE Kenya .....
- [X] KG Kyrgyzstan .....
- [X] KP Democratic People's Republic of Korea .....
- [X] KR Republic of Korea .....
- [X] LS Lesotho .....
- [X] LT Lithuania
- [X] LU Luxembourg
- [X] LV Latvia
- [X] MD Republic of Moldova .....
- [X] MG Madagascar .....
- [X] MK The former Yugoslav Republic of Macedonia .....
- [X] MN Mongolia
- [X] MW Malawi .....
- [X] MX Mexico .....
- [X] NO Norway
- [X] NZ New Zealand .....
- [X] PL Poland .....
- [X] PT Portugal .....
- [X] RO Romania
- [X] RU Russian Federation .....
- [X] SD Sudan
- [X] SE Sweden
- [X] SG Singapore
- [X] SI Slovenia .....
- [X] SK Slovakia .....
- [X] SL Sierra Leone
- [X] TJ Tajikistan .....
- [X] TM Turkmenistan .....
- [X] TR Turkey .....
- [X] TT Trinidad and Tobago .....
- [X] UA Ukraine .....
- [X] UG Uganda .....
- [X] US United States of America .....
- [X] UZ Uzbekistan .....
- [X] VN Viet Nam .....
- [X] YU Yugoslavia .....
- [X] ZW Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after

Precautionary Designation Statement: [illegible] the applicant makes under Rule 4.9(b) all designations which would be permitted under the PCT on the date of the Supplemental Box as being excluded [illegible]

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 05 Feb 99 (05.02.99)	9902459.8	GB		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s) item (1)

* *Where the earlier application is an ARIPO application it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii))* See Supplemental Box

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two letter code may be used)*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	4
description (excluding sequence listing part)	39
claims	4
abstract	1
drawings	
sequence listing part of description	
Total number of sheets	48

Figure of the drawings which should accompany the abstract: 1

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)

T. Bryant

BRYANT, Tracey
AGENT FOR APPLICANT

For receiving Office use only

1 Date of actual receipt of the purported international application

3 Corrected date of actual receipt due to late but [illegible]

2 Drawings:

☐ received

ZENECA CASE PHM.70471/WO

POWER OF ATTORNEY CONCERNING A GIVEN INTERNATIONAL APPLICATION PATENT COOPERATION TREATY

The undersigned applicants ZENECA LIMITED of 15 Stanhope Gate, London W1Y 6LN, United Kingdom and ALAN WELLINGTON FAULL and JASON KETTLE hereby appoint:

KEVIN BILL
TRACEY BRYANT
PAUL MILLINGTON DENERLEY
ALLEN FRANK GILES
JOHN RICHARD MACK
IAN GORDON BERRY
LAURENCE DAVID SCOTT GAINEY
NEIL GODFREY ALASDAIR PHILLIPS
STEPHEN COLLYER SMITH
BRIAN STEELE TAIT
RACHEL MARIA TINSLEY
ANDREW STEPHEN BROWN
DAVID ERIC GILES

All of : Global Intellectual Property
AstraZeneca PLC
Mereside
Alderley Park, Macclesfield
Cheshire, SK10 4TG,
United Kingdom

as Agent to act on their behalf before the competent International Authorities in connection with the International Application concerning:

CHEMICAL COMPOUNDS

Case No. PHM.70471 WO, filed with the United Kingdom Patent Office and to make or receive payment on their behalf.

ZENECA LIMITED

JOANNE MARGARET MARSHALL
AUTHORISED OFFICER
ZENECA LIMITED
Place: Macclesfield, Cheshire.
Date:

Alan Wellington Faull
ALAN WELLINGTON FAULL
Place: Macclesfield, Cheshire
Date: 5th Jan 2000

Copy Sent to Dec

PCT/GB00/0026

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

BRYANT, Tracey
AstraZeneca
Global Intellectual Property
P.O. Box 272
Mereside, Alderley Park
Macclesfield Cheshire SK10 4T
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 10 August 2000 (10.08.00)	
Applicant's or agent's file reference PHM 70471/WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB00/00260	**International filing date** (day/month/year) 31 January 2000 (31.01.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ASTRAZENECA UK LIMITED 15 Stanhope Gate London W1Y 6LN United Kingdom	GB	GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address	State of Nationality	State of Residence
ASTRAZENECA AB S 151 85 Södertälje Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office [X] the designated Offices concerned

[illegible]

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer [illegible]

PCT/GB00/00260

PATENT COOPERATION TREATY

16 MAY 2000 Copy

PCT

From the INTERNATIONAL BUREAU

To:

BRYANT, Tracey
Global Intellectual Property,
Patents
AstraZeneca Uk Limited
Mereside, Alderley Park
Macclesfield Cheshire SK10 4TG
ROYAUME-UNI

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year)
05 May 2000 (05.05.00)

Applicant's or agent's file reference
PHM 70471/WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/00260

International filing date (day/month/year)
31 January 2000 (31.01.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
ZENECA LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
ASTRAZENECA UK LIMITED
15 Stanhope Gate
London W1Y 6LN
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. [illegible]

The International Bureau of WIPO
34, chemin des Colombettes

09/889515

APPLICATION UNDER UNITED STATES PATENT LAWS

JC18 Rec'd PCT/PTO 18 JUL 2001

Atty. Dkt. No. PW 028149 4 / 70471 US1
(M#)

Invention: ANTI-INFLAMMATORY INDOLE DERIVATIVES

Inventor (s): FAULL, Alan Wellington
KETTLE, Jason

Pillsbury Winthrop LLP
Intellectual Property Group
1600 Tysons Boulevard

McLean, VA 22102
Attorneys
Telephone: (703) 905-2000

This is a:

- ☐ Provisional Application
- ☐ Regular Utility Application
- ☐ Continuing Application
  - ☒ The contents of the parent are incorporated by reference
- ☒ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application
- ☐ Substitute Specification
  Sub Spec Filed
  in App. No. /
- ☐ Marked up Specification re
  Sub Spec. filed
  In App No /

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PHM 70471/WO		
International application No.	International filing date *(day, month, year)*	(Earliest) Priority Date *(day, month, year)*
PCT/GB 00/00260	31/01/2000	05/02/1999
Applicant		
ZENECA LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1 **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2 [ ] **Certain claims were found unsearchable** (See Box I)

3 [ ] **Unity of invention is lacking** (see Box II)

4 With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

ANTI-IMFLAMMATORY INDOLE DERIVATIVES

5 With regard to the **abstract**,

[illegible]

INTERNATIONAL SEARCH REPORT

[redacted] national Application No
PCT/GB 00/00260

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42 C07D409/14 C07D403/12 C07D401/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 288 743 A (BROOKS ET. AL.) 22 February 1994 (1994-02-22) column 2, line 16 - line 21; claims; examples	1-10
A	WO 93 12780 A (MERRELL DOW PHARMACEUTICALS) 8 July 1993 (1993-07-08) cited in the application claims; examples	1-10
P,Y	WO 99 07351 A (ZENECA) 18 February 1999 (1999-02-18) cited in the application page 18, line 17 -page 19, line 7; claims; examples	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/00260

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No
P,Y	WO 99 07678 A (ZENECA) 18 February 1999 (1999-02-18) cited in the application page 17, line 8 - line 17; claims; examples	1-10
P,X	WO 99 33800 A (HOECHST) 8 July 1999 (1999-07-08) claims	1,7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/00260

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5288743 A	22-02-1994	MX 9307185 A	31-08-1994
		WO 9412179 A	09-06-1994
WO 9312780 A	08-07-1993	US 5318985 A	07-06-1994
		AT 185969 T	15-11-1999
		AU 3150993 A	28-07-1993
		CA 2124799 A	08-07-1993
		DE 69230224 D	02-12-1999
		DE 69230224 T	13-04-2000
		EP 0617616 A	05-10-1994
		JP 7504890 T	01-06-1995
		NZ 246114 A	26-10-1995
		US 5489579 A	06-02-1996
WO 9907351 A	18-02-1999	AU 8638198 A	01-03-1999
		NO 20000573 A	04-02-2000
WO 9907678 A	18-02-1999	AU 8638098 A	01-03-1999
WO 9933800 A	08-07-1999	AU 2052899 A	19-07-1999

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 00/00260

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42 C07D409/14 C07D403/12 C07D401/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where tical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 288 743 A (BROOKS ET. AL.) 22 February 1994 (1994-02-22) column 2, line 16 - line 21; claims; examples	1-10
A	WO 93 12780 A (MERRELL DOW PHARMACEUTICALS) 8 July 1993 (1993-07-08) cited in the application claims; examples	1-10
P,Y	WO 99 07351 A (ZENECA) 18 February 1999 (1999-02-18) cited in the application page 18, line 17 -page 19, line 7; claims; examples	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-

11 May 2000

18/05/2000

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 00/00260

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 99 07678 A (ZENECA) 18 February 1999 (1999-02-18) cited in the application page 17, line 8 - line 17; claims; examples	1-10
P,X	WO 99 33800 A (HOECHST) 8 July 1999 (1999-07-08) claims	1,7

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 00/00260

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5288743	A	22-02-1994	MX	9307185 A	31-08-1994
			WO	9412179 A	09-06-1994
WO 9312780	A	08-07-1993	US	5318985 A	07-06-1994
			AT	185969 T	15-11-1999
			AU	3150993 A	28-07-1993
			CA	2124799 A	08-07-1993
			DE	69230224 D	02-12-1999
			DE	69230224 T	13-04-2000
			EP	0617616 A	05-10-1994
			JP	7504890 T	01-06-1995
			NZ	246114 A	26-10-1995
			US	5489579 A	06-02-1996
WO 9907351	A	18-02-1999	AU	8638198 A	01-03-1999
			NO	20000573 A	04-02-2000
WO 9907678	A	18-02-1999	AU	8638098 A	01-03-1999
WO 9933800	A	08-07-1999	AU	2052899 A	19-07-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PHM 70471/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00260	31/01/2000	05/02/1999

International Patent Classification (IPC) or national classification and IPC
C07D209/42

Applicant
ASTRAZENECA AB et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00260

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-39 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	10 see below

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this report.

US-A-5,288,743	(A)
WO-A-99 33800	(B)
WO-A-99 07678	(C)
WO-A-99 07351	(D)

The novel feature of the indole derivative of claim 1 is the R4 group, representing an acylamino, sulfonylamino or aminocarbonyloxy group, present at the 4-position of the ring. The dependent claims 2-7, as well as claim 8 drawn to a process for the preparation of compounds of claim 1, and claims 9 and 10 drawn to pharmaceutical compositions containing compounds of claim 1 and compounds of claim1 for use in the preparation of medicaments are novel by consequence. Claims 1 to 10 therefore meet the Novelty requirements of Article 33(2) PCT.

Document (A) represents the closest prior art. This document describes some 1-benzyl-2-carboxyalkyl-5-(heterocyclylmethoxy)- indoles and their use for the inhibition of leukotriene synthesis. the compounds of document (A) are useful for the treatment of inflammation (see column 2, lines 15-20). The presently claimed compounds also have anti-inflammation activity, and differ from the compounds of document (A) through the absence of an alkyl group linking the carboxy group to the 2-position, and through the presence of the R4 group as defined above at the 4-position of the indole ring. Hence the presently claimed compounds are not structurally close to the compounds of document (A), and it would not have been obvious for the skilled man to prepare them in order to make available further anti-inflammation compounds. Inventive step (Article 33(3) PCT) is recognise because the problem of providing further anti-inflammation compounds has been solved in a non obvious manner.

For the assessment of the present claim 10 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can

compound in medical treatment, but may allow, however, claims to a known compound

for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

At present no priority document is available. The examination has been carried out assuming that the priority date is validly claimed. If during the subsequent procedure (e.g. EPO examination) the priority date is found to be invalid for some or all of the presently claimed subject matter, the intermediate documents (B)-(D) may be taken into consideration for the evaluation of Novelty and inventive step.

VII CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents (A) and (B) is not mentioned in the description, nor are these documents identified therein.

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION.

Claim 1 contains several non-limiting definitions such as "optionally substituted aryl" and "optionally substituted heteroaryl", etc. which embrace substitution by any known organic group without limitation on size or number of reactive groups which can be present. The term "heteroaryl" itself embraces any known aromatic heterocyclic group. It is known in pharmaceutical chemistry that small structural changes to heterocyclic rings can lead to considerable changes in a pharmacological activity, or to compounds with a completely different activity. The skilled man would therefore not be able to predict if all compounds falling within the said definition "heteroaryl" would actually solve the problem underlying the present application (i.e. the provision of MCP-1 inhibitors). Also, since the term "functional group" appears to embrace any reactive group and is not limited to the groups suggested on page 4, lines 10-14, it is not clear if the presence of any "functional group" at R4-R7 would give rise to a compound which binds to a MCP-1 receptor, because some reactive groups would be expected to react at competing binding sites.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 209/42, 409/14, 403/12, 401/12, A61K 31/40

A1

(11) International Publication Number: WO 00/46195

(43) International Publication Date: 10 August 2000 (10.08.00)

(21) International Application Number: PCT/GB00/00260

(22) International Filing Date: 31 January 2000 (31.01.00)

(30) Priority Data:
9902459.8 5 February 1999 (05.02.99) GB

(71) Applicant (*for all designated States except US*): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

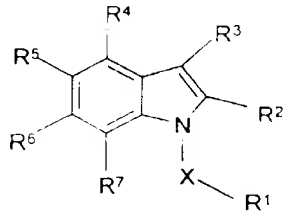
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): FAULL, Alan, Wellington [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). KETTLE, Jason [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: BRYANT, Tracey; Global Intellectual Property, Patents, AstraZeneca UK Limited, Mereside, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ANTI INFLAMMATORY INDOLE DERIVATIVES



(I)

(57) Abstract

Therapeutic compounds of formula (I) wherein X is CH_2 or SO_2; R^1 is an optionally substituted aryl or heteroaryl ring; R^2 and R^3 are various specified groups, R^4 is a group $NHCOR^{15}$, $NHSO_2R^{15}$ or $OCONR^{16}R^{17}$ where R^{15} is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl and R^{16} and R^{17} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, with the proviso that at least one of R^{16} or R^{17} is other than hydrogen, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms, and R^5, R^6 and R^7 are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclic groups; and further provided that when R^4 is a group $NHCOR^{15}$, R^{15} is substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; as well as pharmaceutical compositions containing them are described and claimed. These compounds and compositions are useful in the treatment of disease mediated by monocyte chemoattractant protein-1 or RANTES (Regulated Upon Activation, Normal T cell Expressed and Secreted), such as inflammatory disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
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CN	China	**KZ**	Kazakstan	**PT**	Portugal		
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CZ	Czech Republic	**LI**	Liechtenstein	**RU**	Russian Federation		
DE	Germany	**LK**	Sri Lanka	**SD**	Sudan		
DK	Denmark	**LR**	Liberia	**SE**	Sweden		
EE	Estonia			**SG**	Singapore		

ANTI-INFLAMMATORY INDOLE DERIVATIVES

The present invention relates to chemical compounds, to their production as well as to pharmaceutical compositions containing them as well as to their use in therapy, in particular of inflammatory disease.

MCP-1 is a member of the chemokine family of pro-inflammatory cytokines which mediate leukocyte chemotaxis and activation. MCP-1 is a C-C chemokine which is one of the most potent and selective T-cell and monocyte chemoattractant and activating agents known. MCP-1 has been implicated in the pathophysiology of a large number of inflammatory diseases including rheumatoid arthritis, glomerular nephritides, lung fibrosis, restenosis (International Patent Application WO 94/09128), alveolitis (Jones et al., 1992, *J. Immunol.*, **149**, 2147) and asthma. Other disease areas where MCP-1 is thought to play a part in their pathology are atherosclerosis (e.g. Koch et al., 1992, *J. Clin. Invest.*, **90**, 772 -779), psoriasis (Deleuran et al., 1996, *J. Dermatological Science*, **13**,. 228-236), delayed-type hypersensitivity reactions of the skin, inflammatory bowel disease (Grimm et al., 1996, *J. Leukocyte Biol.*, **59**,. 804-812), multiple sclerosis and brain trauma (Berman et al, 1996, *J. Immunol.*, **156**,. 3017-3023). An MCP-1 inhibitor may also be useful to treat stroke, reperfusion injury, ischemia, myocardial infarction and transplant rejection.

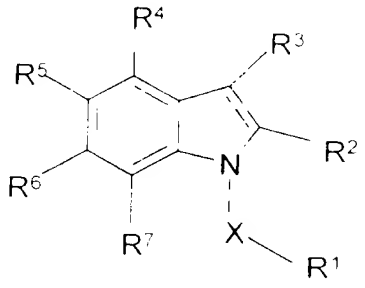
MCP-1 acts through the MCP-1 receptor (also known as the CCR2 receptor). MCP-2 and MCP-3 may also act, at least in part, through the MCP-1 receptor. Therefore in this specification, when reference is made to "inhibition or antagonism of MCP-1" or "MCP-1 mediated effects" this includes inhibition or antagonism of MCP-2 and/or MCP-3 mediated effects when MCP-2 and or MCP-3 are acting through the MCP-1 receptor.

Copending International Patent Application Nos. PCT/GB98/02340 and PCT/GB98/02341 describe and claim groups of compounds based upon the indole ring structure which are inhibitors of MCP-1 and therefore have applications in therapy.

The use of certain indole derivatives as NMDA antagonists is described is USP5051442, WO9312780, JP-483881. Other indoles and their use as inhibitors of

The applicants have found a particular substitution on the indole ring produces advantageous results when used therapeutically as inhibitors of MCP-1.

According to the present invention there is provided a compound of formula (I)

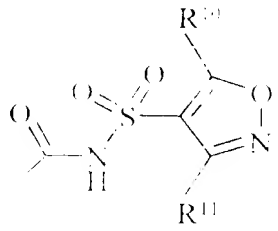


(I)

X is CH_2 or SO_2

R^1 is an optionally substituted aryl or heteroaryl ring;

R^2 is carboxy, cyano, $-C(O)CH_2OH$, $-CONHR^9$, $-SO_2NHR^9$, tetrazol-5-yl, SO_2H, or a group of formula (VI)



(VI)

where R^9 is selected from hydrogen, alkyl, aryl, cyano, hydroxy, $-SO_2R^{12}$ where R^{12} is alkyl, aryl, heteroaryl, or haloalkyl, or R^9 is a group $-(CHR^{13})_r-COOH$ where r is an integer of 1-3 and each R^{13} group is independently selected from hydrogen or alkyl; R^{10} is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally subtituted heteroaryl such as 5 or 6 membered heteroaryl groups, or a group COR^{14} where R^{14} is alkyl,

R^2 is hydrogen, a functional group, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkoxy, optionally substituted aralkyl, optionally substituted aralkyloxy, optionally substituted cycloalkyl;

R^4 is a group $NHCOR^{15}$, $NHSO_2R^{15}$ or $OCONR^{16}R^{17}$ where R^{15} is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl and R^{16} and R^{17} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, with the proviso that at least one of R^{16} or R^{17} is other than hydrogen, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms; and

R^5, R^6 and R^7 are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclic groups.

Suitably, where R^4 is a group $NHCOR^{15}$, R^{15} is substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl.

Compounds of formula (I) are inhibitors of monocyte chemoattractant protein-1. In addition, they appear to inhibit RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted), induced chemotaxis. RANTES is another chemokine from the same family as MCP-1, with a similar biological profile, but acting though the CCR1 receptor. As a result, these compounds can be used to treat disease mediated by these agents, in particular inflammatory disease.

In this specification the term 'alkyl' when used either alone or as a suffix includes straight chained, branched structures. These groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Terms such as "alkoxy" comprise alkyl groups as is understood in the art.

"Halide" includes [illegible] to 8 ring atoms, at least one of which is a heteroatom, such as oxygen, sulphur or nitrogen.

Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

"Heteroaryl" refers to those groups described above which have an aromatic character. The term "aralkyl" refers to aryl substituted alkyl groups such as benzyl.

Other expressions used in the specification include "hydrocarbyl" which refers to any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl.

The term "functional group" refers to reactive substituents. They may comprise electron-donating or electron-withdrawing. Examples of such groups include halo, cyano, nitro, $C(O)_nR^{18}$, OR^{19}, $S(O)_nR^{18}$, $NR^{19}R^{20}$, $C(O)NR^{19}R^{20}$, $OC(O)NR^{19}R^{20}$, $-NR^{19}C(O)_nR^{18}$, $-NR^{19}CONR^{19}R^{20}$, $-N=CR^{19}R^{20}$, $S(O)_mNR^{19}R^{20}$ or $-NR^{19}S(O)_mR^{18}$ where R^{18}, R^{19} and R^{20} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{19} and R^{20} together form an optionally substituted ring which optionally contains further heteroatoms such as $S(O)_m$, oxygen and nitrogen, n is an integer of 1 or 2, m is 1 or 2.

Suitable optional substituents for hydrocarbyl groups R^{18}, R^{19} and R^{20} include halo, perhaloalkyl such as trifluoromethyl, mercapto, hydroxy, carboxy, alkoxy, heteroaryl, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyalkoxy, aryloxy (where the aryl group may be substituted by halo, nitro, or hydroxy), cyano, nitro, amino, mono- or di-alkyl amino, oximino or $S(O)_nR^{21}$ where n is as defined above and R^{21} is alkyl such as C_{1-4} alkyl.

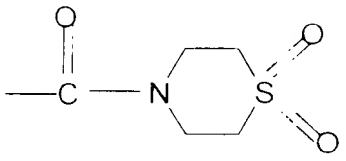
Suitable substituents for these hydrocarbyl or heterocylic groups include those listed above for R^{18}, R^{19} and R^{20}.

Suitably R^1 is an optionally substituted phenyl, pyridyl, naphthyl, furyl or thienyl ring, and in particular is a substituted phenyl or pyridyl ring.

Suitable optional substitutents for R^1 in formula (I) include alkyl, alkenyl, alkynyl, halo, haloalkyl including perhaloalkyl such as trifluoromethyl, mercapto, alkoxy, haloalkoxy, alkenyloxy, alkynyloxy, hydroxyalkoxy, alkoxyalkoxy, alkanoyl, alkanoyloxy, cyano, nitro,

[illegible]

the amide derivative thereof; alkoxy; aryloxy; aralkyloxy; or an amino group which is optionally substituted with alkyl, aryl or aralkyl. A specific functional group which is suitable for R^4, R^5, R^6 and or R^7 is a group of sub-formula (IV).



(IV)

Particular examples of groups R^5, R^6 and R^7 are hydrogen, hydroxy, halo or alkoxy. In particular R^6 and R^7 are hydrogen. R^5 may be hydrogen but in addition is suitably a small subsitutent such as hydroxy, halo or methoxy.

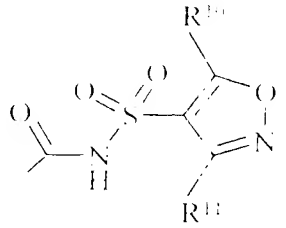
Particular substituents for R^1 include trifluoromethyl, C_{1-4}alkyl, halo, trifluoromethoxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, nitro, carbamoyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, sulphonamido, carbamoylC_{1-4}alkyl, *N*-(C_{1-4}alkyl)carbamoylC_{1-4}alkyl, *N*,*N*-(C_{1-4}alkyl)$_2$carbamoyl-C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyC_{1-4}alkyl.

Additionally or alternatively, two such substituents together may form a divalent radical of the formula -O(CH_2)$_{1-2}$O- attached to adjacent carbon atoms on the R^1 ring.

Preferred substitutents for R^1 are one or more non-polar substituents such as halo.

In particular, R^1 is substituted by one or more halo groups, in particular chlorine. A particular example of an R^1 group is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 2,3-dichloropyrid-5-yl.

Examples of groups R^8 include carboxy; cyano; tetrazol-5-yl; SO_3H; -$CONHR^9$ where R^9 is selected from cyano, hydroxy, -SO_2R^{11} where R^{11} is alkyl such as C_{1-4}alkyl, aryl such as phenyl, heteroaryl or trifluoromethyl, or R^8 is a group-(CHR^{10})$_r$-COOH where r is an integer of 1-3 and each R^{10} group is independently selected from hydrogen or alkyl such as C_{1-4}alkyl; or R^8 is a group -SO_2NHR^{11} where R^{11} is an optionally substituted phenyl or an optionally



(VI)

where R^{13} and R^{14} are independently selected from hydrogen or alkyl, particularly C_{1-4} alkyl.

Preferably R^2 is carboxy or a pharmaceutically acceptable salt or ester thereof.

Suitable groups R^3 include hydrogen, fluoro, chloro, bromo, iodo, methyl, cyano, trifluoromethyl, hydroxymethyl, alkoxyalkyl such as C_{1-4}alkoxymethyl, methoxy, benzyloxy, carboxyalkoxy such as carboxymethoxy, methylsulphanyl, methylsulphinyl, methylsulphonyl or carboxyC_{3-6}cycloalkyl, -$(CHR^{22})_r$-$NR^{23}R^{24}$ (where r is 0-2, each R^{22} is independently hydrogen or alkyl, in particular C_{1-4} alkyl, R^{23} and R^{24} are independently selected from H and C_{1-4}alkyl or R^{23} and R^{24} together with the nitrogen to which they are attached form a 5 or 6 membered ring optionally containing one further heteroatom selected from O, N, S, S(O) or SO_2. Suitably R^{23} and R^{24} together form a heterocylic ring such as morpholino or piperazinyl.

Other such groups R^3 include optionally substituted aryl groups, such as optionally substituted phenyl or naphthyl group. Suitable substituents for phenyl groups R^3 include one or more groups selected from chlorine, fluorine, methyl, trifluoromethyl, trifluoromethoxy, amino, formyl, phenyl, methoxy, phenoxy or phenyl.

R^3 may comprise a range of substituents as listed above, in particular, hydrogen or a small substituent group such as C_{1-4}alkyl in particular methyl, or trifluoromethyl, and is preferably hydrogen.

Suitable optional substitutents for the group R^{15}, R^{16} and R^{17} as they appear in the definition of R4, include functional groups as hereinbefore defined, as well as aryl or heterocyclyl groups, either of which may themselves be substituted by one or more functional groups or further aryl or heterocyclyl groups.

[illegible] optionally substituted for example [illegible]

pyridyl; pyrimidinyl; phenyl optionally substituted by halo such as chloro, hydroxy, alkoxy such as methoxy, carbamoyl, acyl such as acetyl, or hydroxyalkyl where the alkyl group suitably includes at least two carbon atoms, such as hydroxyethyl. Other examples of subsitutents for phenyl groups R^{15} is alkanoylamino group such as methoylamino.

Where R^{15}, R^{16} and/or R^{17} is a heterocyclyl group, or where R^{16} and R^{17} together form an optionally substituted heterocyclic ring, these may be substituted by functional groups such as halo or hydroxy, or by alkyl groups such as methyl or ethyl, or alkenyl or alkynyl groups any of which may be subsituted, for example with hydroxy, as well as with further heteroaryl groups such as pyridyl. Particular examples of heterocyclic groups R^{15}, R^{16} and/or R^{17} are optionally substituted thiophenyl, optionally substituted imidazolyl, optionally subtituted pyridyl.

Thus thiophenyl groups R^{15}, R^{16} and or R^{17} may comprise pyridyl-thiophenyl, whilst an example of a substituted imidazolyl group for R^{15}, R^{16} and/or R^{17} is methylimidazolyl and halopyridyl in particular chloropyridyl is an example of a substituted pyridyl moiety for these groups.

Particular examples of R^{15} include alkyl in particular methyl optionally substituted by a functional groups or, in particular, a heterocyclyl group where the heterocyclyl group may be optionally substituted by a functional group such as halo or hydroxy or by an alkyl group such as methyl. Preferably, R^{15} is a substituted alkyl group. Where the substitutent is a functional group, it is preferably a group of formula $NR^{19}R^{20}$ where R^{19} and R^{20} are as defined above. Thus examples of substituted alkyl groups R^{15} include morpholinomethyl or alkyl such as methyl substituted with a substituted alkyl amino group wherein the substitutents include carboxy, alkanoyl, phenyl or alkyl sulphonyl.

Other examples of R^{15} are heterocyleyl groups which are optionally subsitituted for example by alkyl such as methyl, functional groups such as chloro or heterocyeyl groups such as pyridyl.

Particular examples of R^{16} and R^{17} are alkyl such as methyl.

X is CH or SO and is preferably CH.

[illegible] are base salts such as an alkali metal salt for example sodium or potassium or alkaline earth metal salt for

example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N*,*N*-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a sodium salt.

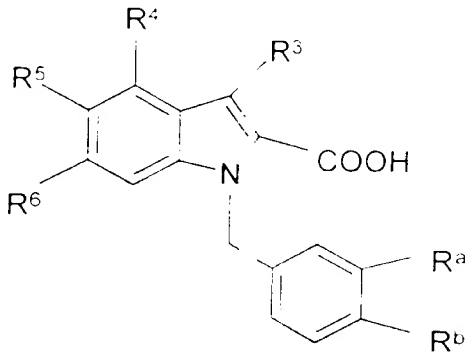
An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

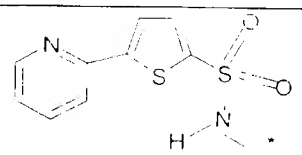
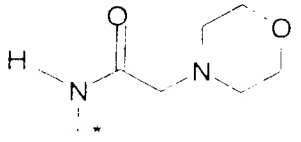
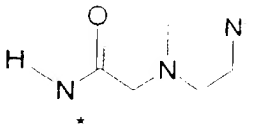
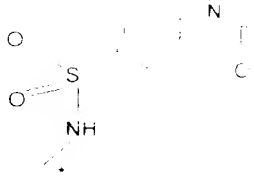
Suitable pharmaceutically acceptable esters for carboxy include alkyl esters, such as C_{1-6} alkyl esters for example, ethyl esters, C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxy-carbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

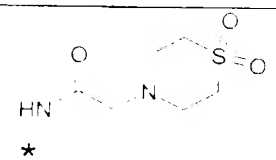
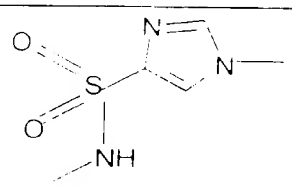
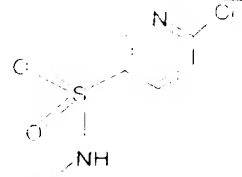
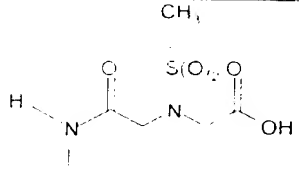
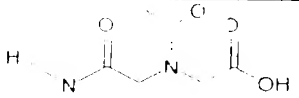
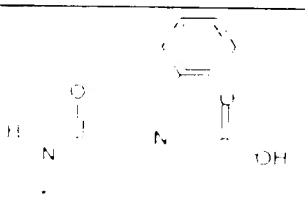
Suitable pharmaceutically acceptable esters of compounds of formula (I) are *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

Esters which are not *in vivo* hydrolysable are useful as intermediates in the production of the compounds of formula (I) and therefore these form a further aspect of the invention.

Table 1



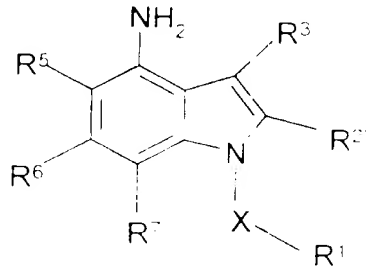
Compd No.	R^3	R^4	R^5	R^6	R^a	R^b
1	H		H	H	H	H
2	H		H	H	Cl	Cl
3	H		H	H	Cl	Cl
4	H		H	H	Cl	Cl
5	H		H	H	Cl	Cl

6	H		H	H	Cl	Cl
7	H		H	H	Cl	Cl
8	H	$NHC(O)CH_2NHCH_2COOH$	H	H	Cl	Cl
9	H		H	H	Cl	Cl
10	H	$OC(O)N(CH_3)_2$	H	H	Cl	Cl
11	H		H	H	Cl	Cl
12	H		H	H	Cl	Cl
13	H		H	H	Cl	Cl
14	H	$NHC(O)CH_2N(CH_3)CH_2COOH$	H	H	Cl	Cl
15	H		H	H	Cl	Cl

Where * indicates the point of attachment of the group to the rest of the molecule.

Compounds of formula (I) are suitably prepared by methods such as those described in International Patent Application Nos. PCT GB98 02340 and PCT GB98 02341.

In particular compounds of formula (I) where R^4 is $NHCOR^{15}$ or $NHSO_2R^{15}$ can be prepared by reacting a compound of formula (VII)



(VII)

where X, R^1, R^3, R^5, R^6 and R^7 are as defined in relation to formula (I), R^2 is a group R^2 as defined in relation to formula (I) or a protected form thereof, with a compound of formula (VIII)

$$Z\text{-}R^{22}$$

(VIII)

where Z is a leaving group and R^{22} is a group $COR^{15'}$ or $SO_2R^{15'}$ where $R^{15'}$ is group R^{15} as defined in relation to formula (I) or a precursor thereof;

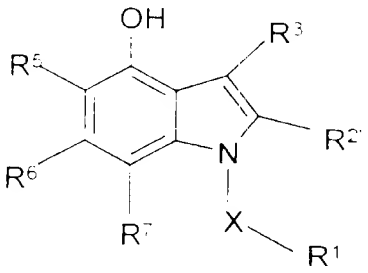
and thereafter if desired or necessary:

(i) converting a precursor group $R^{15'}$ to a group R^{15} and/or converting a group R^{15} to a different such group;

(ii) deprotecting a group $R^{2'}$ to a group R^2.

Suitable leaving groups Z include halo such as chloro.

The reaction is suitably effected in an organic solvent such as dichloromethane or tetrahydrofuran in the presence of a base such as triethylamine or pyridine. Moderate temperatures, for example from 0° to 50° C and conveniently ambient temperature, are



(VIIA)

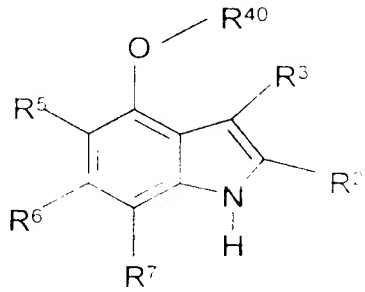
where X, R^2, R1, R^3, R^5, R^6 and R^7 are as defined in relation to formula (I), R^2 is a group R^2 as defined in relation to formula (I) or a protected form thereof, with a compound of formula (VIIIA)

$$Z\text{-}CONR^{16}R^{17}$$

(VIIIA)

where Z, R^{16} and R^{17} are as defined above.

Compounds of formula (VIIA) can be prepared by reacting a compound of formula (IX)



(IX)

where R1, R2, R3 and R5 are as defined in relation to formula (I) and R6 is as defined in relation to formula (VII) and R40 is a protecting group; with a compound of formula (X)

$$R^1\text{-}X\text{-}Z^1$$

thereafter [illegible] group R40

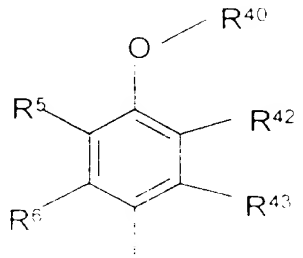
Suitable leaving groups for Z include halide such as chloride, bromide or iodide, as well as mesylate or tosylate. The reaction is suitably effected in an organic solvent such as dimethylformamide (DMF) tetrahydrofuran (THF) or DCM in the presence of a base such as sodium hydride, sodium hydroxide, potassium carbonate. Optionally the reaction is effected in the presence of a suitable phase transfer catalyst. The choice of base and solvent is interdependent to a certain extent in that certain solvents are compatible with some bases only as is understood in the art. For example, sodium hydride may preferably be used with dimethylformamide or tetrahydrofuran and sodium hydroxide is preferably used with dichloromethane and a phase transfer catalyst.

The reaction can be carried out at moderate temperatures, for example from 0 to 50°C and conveniently at about ambient temperature.

Preferably, R^1 is an ester group in the compound of formula IX and this may be subsequently converted to an acid or to another ester or salt, by conventional methods later in the process. For example, when X is a group SO_2 and R^2 is a methyl ester of carboxy, it may be converted to the corresponding carboxylic acid by reaction with lithium iodide in dry pyridine or DMF.

Suitable protecting groups R^{40} include acetyl or benzyl. The reaction conditions employed will be variable depending upon the nature of the protecting group R^{40} and would be apparent to a skilled person. Acetyl groups may be removed by reaction with a strong base such as sodium methoxide, whereas benzyl groups may be removed by hydrogenation for example in the presence of a catalyst such as a palladium catalyst.

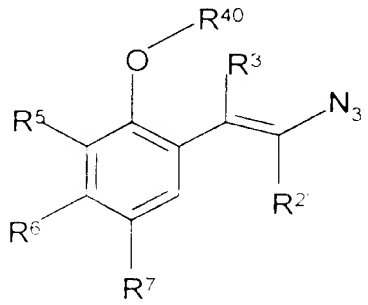
Compounds of formula (IX) may be prepared by cyclisation of a compound of formula (XII)



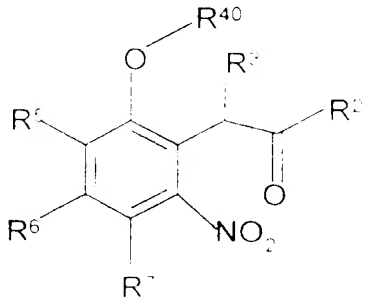
where R^5, R^6, R^7 and R^{40} are as defined above and R^{42} and R^{43} represent a combination of moieties which can cyclise to form an appropriately substituted pyrrole ring. For example, one of R^{42} and R^{43} can be a group of formula $-CH=C(R^{44})N_3$ where R^{44} is a group R^2 as defined above, or a protected form thereof, and the other may be hydrogen. Cyclisation to form a compound of formula (XII) may then be effected by heating for example under reflux in an organic solvent, in particular a high boiling aprotic solvent such as xylene or toluene.

Alternatively, one of R^{42} and R^{43} may be nitro and the other may be a group of formula $-CH_2C(O)R^{45}$ where R^{45} is as defined above in relation to formula (VII). These compounds will cyclise in the presence of a catalyst such as palladium on carbon in the presence of hydrogen. The reaction may be effected at moderate temperatures for example of from 0 to 80°C, conveniently at about ambient temperature.

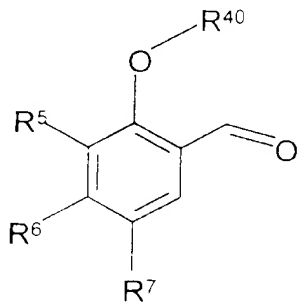
Thus examples of compounds of formula (XII) include compounds of formula (XIII) and (XIV)



(XIII)



Compounds of formula (XIII) where R^5 is hydrogen may be prepared for example by reacting a compound of formula (XV)



(XV)

with a compound of formula (XVI)

$$N_3CH_2R^{2'}$$

(XVI)

where R^5, R^6, R^7, and $R^{2'}$ are as defined hereinbefore. The reaction may be effected in an organic solvent such as ethanol at low temperatures of from -20 to 0°C, suitably at about 0°C. The reaction is suitably effected in the presence of a base such as an alkoxide, in particular an ethoxide, for example potassium ethoxide.

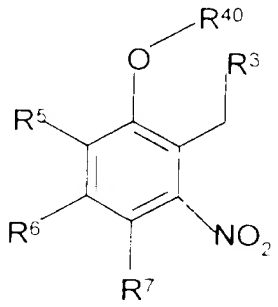
Compounds of formula (XVI) are suitably prepared by reacting a compound of formula (XVII)

$$R_4CH_2R^{2'}$$

(XVII)

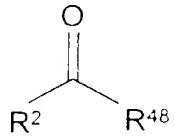
where $R^{2'}$ is defined above and $R^{4'}$ is a leaving group such as halide and in particular bromide, with an azide salt, such as an alkali metal azide salt in particular sodium azide.

Compounds of formula (XIV) may be prepared by reacting a compound of formula (XVIII)



(XVIII)

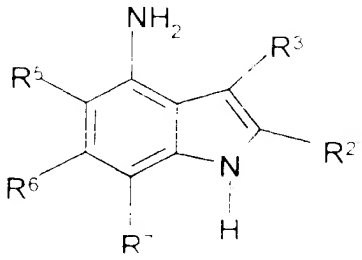
where R^5, R^6, R^7, R^3, R^{40} and R^2 are as defined above, with a compound of formula (XIX)



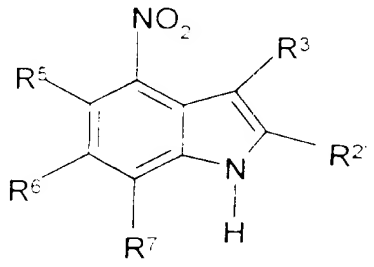
(XIX)

where R^2 is as defined above and R^{48} leaving group such as hydroxy. Examples of compounds of formula (XVI) are oxalates such as diethyloxalate. The reaction is suitably effected in the presence of a base such as sodium hydride in an organic solvent such as THF. Moderate temperatures of from 0° to 40°C and conveniently ambient temperature is employed.

Compounds of formula (VII) are suitably prepared using a reaction analogous to that between compounds (IX) and (X), where in place of the compound of formula (IX), a compound of formula (IXA) is employed



reduction of the corresponding nitro compound of formula (XX)



(XX)

where R^2, R^3, R^5, R^6 and R^7 are as defined above.

Compounds of formula (X), (XVI), (XV), (XVII), (XVIII), (XIX) and (XX) are either known compounds or they may be prepared from known compounds by conventional literature methods.

According to a further aspect of the invention there is provided a compound of the formula **(I)** as defined herein, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy. In particular, the compounds are used in methods of treatment of inflammatory disease.

According to a further aspect of the present invention there is provided a method for antagonising an MCP-1 mediated effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

The invention also provides a pharmaceutical composition comprising a compound of formula **(I)** as defined herein, or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof, in combination with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus

for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a

temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of rats.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

A further aspect of the invention comprises the use of a compound of formula (I) as defined above in the preparation of a medicament for the treatment of inflammatory disease.

The invention is further illustrated, but not limited by the following Examples in which the following general procedures were used unless stated otherwise.

Preparation 1

Ethyl *N*-(3,4-dichlorobenzyl)-4-nitroindole-2-carboxylate

Ethyl 4-nitroindole-2-carboxylate (26 g) [prepared according to S. M. Parmerter *et. al* *J. Amer. Chem. Soc.*, 1958, **80**, 4621], 3,4-dichlorobenzyl chloride (16 ml), potassium carbonate (17 g) and potassium iodide (2 g) in DMF (250 ml) were stirred at 60°C for 2 hours. The reaction was concentrated *in vacuo* and the residue partitioned between water and dichloromethane. *Iso*-hexane was added to the combined organic extracts resulting in crystallisation of the product as yellow needles (39 g, 89%) NMR d (CD_3SOCD_3) 1.30 (t, 3H), 4.32 (q, 2H), 5.93 (s, 2H), 6.88 (dd, 1H), 7.18 (d, 1H), 7.52 (d, 1H), 7.56 (dd, 1H), 7.78 (s,

Preparation 2

Ethyl *N*-benzyl-4-aminoindole-2-carboxylate

A mixture of ethyl 4-nitroindole-2-carboxylate (8.2 g), anhydrous potassium carbonate (6.0 g) and benzyl bromide (4.3 ml) in DMF (100 ml) was stirred at 50-60°C for 2 hours. The solvent was evaporated *in vacuo* and the residue partitioned between dichloromethane and water (250 ml each); the organic layer was separated, dried ($MgSO_4$) and evaporated to give a yellow solid (12 g), which was dissolved in a mixture of tetrahydrofuran / ethanol (200 ml, 1:1) and stirred while adding a solution of sodium dithionite (26 g) in water (50 ml). The mixture was stirred for 1 hour at 25°C and partitioned between dichloromethane and water (200 ml each), the organic layer was washed with water (100 ml) and dried ($MgSO_4$). Combined organic extracts were concentrated *in vacuo* and the residue purified by column chromatography using dichloromethane as eluent to give a the product as a brown solid (1.4 g, 14%); NMR d (CD_3SOCD_3) 1.28 (t, 3H), 4.27 (q, 2H), 5.57 (s, 2H), 5.73 (s, 2H), 6.22 (d, 1H), 6.62 (d, 1H), 6.95 - 7.05 (m, 3H), 7.15 - 7.30 (m, 3H), 7.60 (s, 1H).

Preparation 3

Ethyl *N*-(3,4-dichlorobenzyl)-4-nitroindole-2-carboxylate

Sodium hydroxide (3M, 20 ml) was added to a vigorously stirred solution of ethyl 4-nitroindole-2-carboxylate (4 g), 3,4-dichlorobenzyl chloride (4.73 ml) and tetra-*n*-butylammonium hydrogensulphate (0.2 g) in dichloromethane (60 ml). The reaction was stirred for 48 hours then partitioned between 2M HCl and dichloromethane. Combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography using *iso*-hexane : 20% ethyl acetate as eluent to give the product as a yellow crystalline solid (5.26 g, 78%); NMR δ (CD SOCD$_3$) 1.3 (t, 3H), 4.3 (q, 2H), 5.95 (s, 2H), 6.9 (m, 1H), 7.6 (m, 4H), 8.2 (t, 2H); *M/z* (-) 393.3 (*M*$^-$).

Ethyl *N*-(3,4-dichlorobenzyl)-4-aminoindole-2-carboxylate

A solution of ethyl *N*-(3,4-dichlorobenzyl)-4-nitroindole-2-carboxylate (2.41 g) in tetrahydrofuran (100 ml) was stirred in the presence of [illegible]

extract were dried ($MgSO_4$) [illegible] solid

(1.98 g, 89%); NMR d (CD_3SOCD_3) 1.3 (t, 3H), 4.2 (q, 2H), 5.7 (s, 4H), 6.2 (d, 1H), 6.6 (d, 1H), 7.0 (m, 2H), 7.25 (m, 1H),
7.5 (d, 1H), 7.6 (m, 1H); *M/z* (+) 363.3 (MH$^+$).

Preparation 4

Ethyl 4-chloroacetamido-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate

Ethyl 4-amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (2.03 g), chloroacetyl chloride (0.5 ml) and triethylamine (4.0 ml) were stirred in dichloromethane (50 ml) for 16 hours. The reaction was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with toluene to give the product as a pale grey solid (1.61 g, 65%); NMR d (CD_3SOCD_3) 1.28 (t, 3H), 4.30 (q, 2H), 4.40 (s, 2H), 5.81 (s, 2H), 6.88 (dd, 1H), 7.30 (m, 3H), 7.50 (d, 1H), 7.76 (s, 1H), 7.78 (d, 1H), 10.19 (brs, 1H); *M/z* (-) 439 (M$^-$), 437.

Example 1

Compound 2

Ethyl 4-chloroacetamido-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (0.15 g) and morpholine (2.0 ml) were dissolved in methoxyethanol (5.0 ml) and the reaction stirred for 72 hours. The reaction was then poured into water (100 ml) and the resulting solid filtered and dried *in vacuo*. The solid was dissolved in THF (2.5 ml) and methanol (2.5 ml), and to this was added NaOH (3M, 2.0 ml). The reaction was stirred for 16 hours, then concentrated. The residue was dissolved in water, and precipitated by dropwise addition of acetic acid. The resulting solid was filtered and dried *in vacuo* to give the title compound as a white solid (0.1 g, 63%, 2 steps); NMR d (CD_3SOCD_3) 2.58 (t, 4H), 3.29 (s, 2H), 3.65 (t, 4H), 5.82 (s, 2H), 6.90 (dd, 1H), 7.30 (m, 3H), 7.52 (m, 2H), 7.72 (d, 1H), 9.80 (s, 1H); *M/z* (-) 462 (M$^-$), 460, 418.

Example 2

The procedure described in Example 1 above was repeated using the appropriate

Compound 3

49% yield. 2 steps: NMR d (CD_3SOCD_3) 2.27 (s, 3H), 2.54 (t, 4H), 2.62 (t, 4H), 3.22 (s, 2H), 5.84 (s, 2H), 6.95 (dd, 1H), 7.22 (m, 2H), 7.33 (s, 1H), 7.41 (s, 1H), 7.50 (d, 1H), 7.72 (d, 1H), 9.75 (s, 1H); *M/z* (-) 475 (M^-), 473, 429, 109.

Compound 6

14% yield. 2 steps: *M/z* (-) 510 (M^-), 508, 464.

Example 3

Di-ester of Compound 8

Ethyl 4-chloroacetamido-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (0.4 g), glycine methyl ester hydrochloride (0.57 g) and triethylamine (1.25 ml) were dissolved in methoxyethanol (4.0 ml) and the reaction heated at 100°C for 6 hours. The reaction was cooled and partitioned between water and ethyl acetate. Combined organic extracts were dried ($MgSO_4$) and concentrated and the residue purified by chromatography using toluene : ethyl acetate (1:1) as eluent to give the product, ethyl 4-[(*N*-(methoxycarbonylmethyl)-glycyl)amino]-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate, as a pale yellow solid (0.17 g, 38%); NMR d (CD_3SOCD_3) 1.28 (t, 3H), 3.44 (s, 2H), 3.50 (s, 2H), 3.63 (s, 3H), 4.28 (q, 2H), 5.82 (s, 2H), 6.88 (dd, 1H), 7.10 - 7.30 (m, 4H), 7.50 (d, 1H), 7.69 (s, 1H), 7.80 (dd, 1H), 10.00 (brs, 1H); *M/z* (+) 494, 492 (M^+).

Example 4

Di-ester of Compound 11

Methanesulphonyl chloride (0.1 ml) was added to stirred solution of ethyl 4-[(*N*-(methoxycarbonylmethyl)glycyl)amino]-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (0.33 g) and triethylamine (0.47 ml) in dichloromethane (4.0 ml) and the reaction stirred for 3 hours

1.27 (t, 3H), 3.10 (s, 3H), 3.67 (s, 3H), 4.20 (s, 2H), 4.28 (q+s, 2H+2H), 5.82 (s, 2H), 6.87 (dd, 1H), 7.28 (m, 3H), 7.50 (d, 1H), 7.80 (m, 2H), 10.00 (brs, 1H), *M/z* (+) 572, 570 (*M*$^+$).

Example 5

The procedure described in the Example 4 above was repeated using the appropriate acid chloride. Thus was obtained the compound described below.

Di-ester of Compound 12

64% yield; *M/z* (-) 534 (*M*$^-$), 532.

Example 6

Di-ester of Compound 14

Sarcosine ethyl ester hydrochloride (1.23 g) and potassium carbonate (1.11 g) were added to a solution of ethyl 4-chloroacetamido-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (700 mg) in acetone (25 ml), stirred and heated at 65°C overnight. The reaction was partitioned between water (50 ml) and ethyl acetate (50 ml), extracted with ethyl acetate (2 x 50 ml), and dried ($MgSO_4$). The combined organic extracts were concentrated *in vacuo*, and the residue purified by column chromatography using 30% ethyl acetate : toluene as eluent, to afford the product as a yellow solid (768 mg, 92%): NMR d (CD_3SOCD_3) 1.21 (t, 3H), 1.28 (t, 3H), 2.45 (s, 3H), 3.42 (s, 2H), 3.53 (s, 2H), 4.16 (q, 2H), 4.30 (q, 2H), 5.81 (s, 2H), 6.88 (d, 1H), 7.27 (m, 2H), 7.52 (d, 1H), 7.67 (s, 1H), 7.84 (d, 1H), 9.95 (s, 1H), *M/z*(+) 520.3 (*M*H$^+$)

Example 7

The procedure described in Example 6 above was repeated using the appropriate amine. Thus was obtained the compound described below.

Diester of Compound 13

Example 8

Di-ester of Compound 15

A solution of methyl iodide (0.026 ml) in DMF (2 ml) was added to a solution of sodium hydride (15 mg, 60% in mineral oil) and ethyl 4-[(*N*-benzyl-*N*-ethoxycarbonylmethyl)glycyl]amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (the diester of Compound 13) (200 mg) in DMF (4 ml), and stirred under an atmosphere of argon at ambient temperature for 4 hours. The reaction was quenched with water (50 ml) and extracted with ethyl acetate (3 x 50 ml), and the combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to afford the product as a pale brown oil (93 mg, 45%); NMR d (CD_3SOCD_3) 1.05 (t, 3H), 1.30 (t, 3H), 3.21 (s, 2H), 3.28 (s, 3H), 3.41 (s, 2H), 3.70 (s, 2H), 3.93 (q, 2H), 4.30 (q, 2H), 5.84 (s, 2H), 6.90 (d, 1H), 7.01 (d, 1H), 7.07 - 7.40 (m, 8H), 7.48 - 7.64 (m, 2H); *M/z* (+) 610.5 (MH^+).

Example 9

Compound 8

Ethyl 4-[(*N*-(methoxycarbonylmethyl)glycyl]amino]-*N*-(3,4-dichlorobenzyl)indole-2-carboxylate (0.15 g) was dissolved in THF / methanol (1:1) (10 ml) and sodium hydroxide (2M, 2.5 ml) was added and the reaction stirred for 16 hours. The reaction was then concentrated *in vacuo* and the residue dissolved in water. The solution was acidified by dropwise addition of acetic acid, resulting in the precipitation of a white solid which was filtered, washed with water and dried *in vacuo* to give the desired end product as a white solid (108 mg, 79%); NMR d (CD_3SOCD_3) 3.40 (s, 2H), 3.64 (s, 2H), 5.82 (s, 2H), 6.92 (dd, 1H), 7.20 - 7.38 (m, 3H), 7.50 (d, 1H), 7.62 (s, 1H), 7.78 (d, 1H), 10.15 (brs, 1H).

Example 10

Compound 11

79% yield: NMR d (CD_3SOCD_3) 3.10 (s, 3H), 4.02 (s, 2H), 4.20 (s, 2H), 5.83 (s, 2H), 6.88 (dd, 1H), 7.25 (m, 3H), 7.50 (d, 1H), 7.75 (s, 1H), 7.80 (d, 1H), 10.49 (brs, 1H); *M/z* (-) 528 (M^+), 526, 360, 358, 289, 253, 217.

Compound 12

78% yield: NMR d (CD_3SOCD_3) 2.00 (d, 3H), 4.03 (s, 1H), 4.20 (s, 1H), 4.23 (s, 1H), 4.40 (s, 1H), 5.82 (s, 2H), 6.88 (m, 1H), 7.25 (m, 3H), 7.52 (dd, 1H), 7.76 (m, 2H), 10.13 (brs, 1H); *M/z* (-) 492 (M^+), 490, 324, 253, 224.

Compound 14

60% yield: NMR d (CD_3SOCD_3) 2.46 (s, 3H), 3.38 (s, 2H), 3.42 (s, 2H), 5.88 (s, 2H), 6.92 (d, 1H), 7.20 (m, 2H), 7.31 (s, 1H), 7.50 (m, 2H), 7.82 (d, 1H). *M/z* (-) 462.2 (M-H$^+$).

Compound 15

15% yield: NMR d (CD_3SOCD_3) 3.21 (s, 2H), 3.31 (s, 3H), 3.40 (s, 2H), 3.69 (s, 2H), 5.83 (s, 2H), 6.90 (d, 2H), 6.98 (d, 2H), 7.15 (m, 6H), 7.27 (t, 1H), 7.39 (s, 1H), 7.53 (m, 2H); *M/z* (-) 554.3 (M-H$^+$).

Compound 13

25% yield: NMR d (CD_3SOCD_3) 3.44 (s, 2H), 3.46 (s, 2H), 3.85 (s, 2H), 5.91 (s, 2H), 6.87 (m, 1H), 7.13 - 7.36 (m, 6H), 7.40 (m, 2H), 7.53 (m, 2H), 7.78 (d, 1H). *M/z* (-) 538.2 (M-H$^+$), 253.2.

Example 11

***N*-Benzyl-4-(2-(pyrid-2-yl)thiophene-5-sulphonyl))aminoindole-2-carboxylic acid (Compound 1)**

2M. The ethyl acetate layer was concentrated in vacuo and the residue purified by

chromatography on silica using ethyl acetate as eluent, to give a yellow solid which was dissolved in ethanol (50 ml) at 60°C and treated with NaOH (2M, 4.0 ml) with stirring for 2 hours. The solvent was evaporated *in vacuo*, the residue dissolved in water (50 ml) and filtered. The clear yellow filtrate was acidified with 2N HCl and extracted with dichloromethane : methanol (9:1, 100 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a pale brown solid, which was triturated with ether to give the product as an off white powder (150 mg, 63%, 2 steps); NMR d (CD_3SOCD_3) 5.87 (s, 2H), 6.9 - 7.1 (m, 9H), 7.30 (dd, 2H), 7.43 (d, 1H), 7.63 (d, 1H), 7.81 (dd, 1H), 7.96 (d, 1H), 8.50 (d, 1H); *M/z* (-) 488 (*M*-H$^+$).

Example 12

The procedure described in Example 11 above was repeated using the appropriate aminoindole and sulphonyl chloride. Thus were obtained the compounds described below.

4-(4-Acetylaminobenzenesulphonyl)amino-*N*-(3,4-dichlorobenzyl)indole-2-carboxylic acid (Compound 4)

66% yield (2 steps); NMR d (CD_3SOCD_3) 2.00 (s, 3H), 5.75 (s, 2H), 6.80 (dd, 1H), 6.92 (d, 1H), 7.12 (dd, 1H), 7.22 (m, 2H), 7.48 (d, 1H), 7.56 (s, 1H), 7.66 (s, 4H), 10.24 (brs, 1H), 10.45 (brs, 1H); *M/z* (-) 532 (*M*-H$^+$), 530.

***N*-(3,4-Dichlorobenzyl)-4-(2-(pyrid-2-yl)thiophene-5-sulphonyl))aminoindole-2-carboxylic acid (Compound 5)**

69% yield (2 steps); NMR d (CD_3SOCD_3) 5.80 (s, 2H), 6.80 (dd, 1H), 7.0 - 7.5 (m, 8H), 7.68 (d, 1H), 7.83 (dd, 1H), 7.92 (d, 1H), 8.48 (dd, 1H); *M/z* (-) 558 (*M*-H$^+$), 556.

***N*-(3,4-Dichlorobenzyl)-4-(1-methylimidazole-4-sulphonyl)aminoindole-2-carboxylic acid (Compound 7)**

N-(3,4-Dichlorobenzyl)-4-(2-chloropyridyl-5-sulphonyl)aminoindole-2-carboxylic acid (Compound 9)

30% yield (2 steps); NMR d (CD_3SOCD_3) 5.85 (s, 2H), 6.83 (d, 1H), 6.93 (dd, 1H), 7.03 (dd, 1H), 7.15 (d, 1H), 7.20 (s, 1H), 7.26 (s, 1H), 7.46 (d, 1H), 7.60 (d, 1H), 8.05 (dd, 1H), 8.62 (d, 1H); *M/z* (-) 512 (*M*-H$^+$), 510, 508.

Example 13

Methyl *N*-(3,4-dichlorobenzyl)-4-(dimethylcarbamyloxy)indole-2-carboxylate (Methyl ester of Compound 10)

Dimethylcarbamyl chloride (83 mg) was added to a stirred solution of methyl *N*-(3,4-dichlorobenzyl)-4-hydroxyindole-2-carboxylate (150 mg), triethylamine (65 mg) and DMAP (5 mg) in dichloromethane. The reaction was stirred for 16 hours at room temperature under an atmosphere of nitrogen. The reaction was washed with hydrochloric acid (2M, 70 ml), saturated aqueous sodium hydrogencarbonate solution, water and saturated sodium chloride solution. Combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by column chromatography using 60% ethyl acetate : *iso*-hexane as eluent to give the product as a colourless gum (132 mg, 74%); NMR d (CD_3SOCD_3) 2.94 (s, 3H), 3.12 (s, 3H), 3.81 (s, 3H), 5.82 (s, 2H), 6.91 (m, 2H), 7.21 (s, 1H), 7.27 - 7.36 (m, 2H), 7.46 (d, 1H), 7.52 (d, 1H); *M/z* (-) 421 (*M*H$^+$).

Example 14

***N*-(3,4-Dichlorobenzyl)-4-(dimethylcarbamyloxy)indole-2-carboxylic acid (Compound 10)**

Desesterifiation of the compound of Example 13 using the method described in Example 9 above yielded Compound 10.

93% yield; NMR d (CD_3SOCD_3) 2.94 (s, 3H), 3.11 (s, 3H), 5.91 (s, 2H), 6.82 (d, 1H), 6.94 - 7.03 (m, 2H), 7.18 (t, 1H), 7.29 - 7.39 (m, 2H), 7.50 (d, 1H); *M/z* (-) 405 (*M*-H$^+$).

[illegible] present invention

Abbreviations:

ATCC	American Type Culture Collection, Rockville, USA.
BCA	Bicinchroninic acid, (used, with copper sulphate, to assay protein)
BSA	Bovine Serum Albumin
DMEM	Dulbecco's modified Eagle's medium
EGTA	Ethylenebis(oxyethylenenitrilo)tetraacetic acid
FCS	Foetal calf serum
HEPES	(N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid])
HBSS	Hank's Balanced Salt Solution
hMCP-1	Human Monocyte Chemoattractant Protein-1
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction

AMPLITAQ™, available from Perkin-Elmer Cetus, is used as the source of thermostable DNA polymerase.

Binding Buffer is 50 mM HEPES, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% foetal calf serum, adjusted to pH 7.2 with 1 M NaOH.

Non-Essential Amino Acids (100X concentrate) is: L-Alanine, 890 mg/l; L-Asparagine, 1320 mg/l; L-Aspartic acid, 1330 mg/l; L-Glutamic acid, 1470 mg/l; Glycine, 750 mg/l; L-Proline, 1150 mg/l and; L-Serine, 1050 mg/l.

Hypoxanthine and Thymidine Supplement (50x concentrate) is: hypoxanthine, 680 mg/l and; thymidine, 194 mg/l.

Penicillin-Streptomycin is: Penicillin G (sodium salt), 5000 units/ml, Streptomycin sulphate, 5000 µg/ml.

Human monocytic cell line THP-1 cells are available from ATCC, accession number ATCC TIB-202.

Hank's Balanced Salt Solution (HBSS) was obtained from Gibco, see *Proc. Soc. Exp.*

mg/l; $NaHCO_3$ 2000 mg/l & Na_2HPO_4 (anhyd) 800 mg/l], D-Glucose 2000 mg/l, reduced glutathione 1 mg/l, amino acids and vitamins.

FURA-2/AM is 1-[2-(5-carboxyoxazol-2-yl)-6-aminobenzofuran-5-oxy]-2-(2'-amino-5'-methylphenoxy)-ethane-*N,N,N',N'*-tetraacetic acid pentaacetoxymethyl ester and was obtained from Molecular Probes, Eugene, Oregon, USA.

Blood Sedimentation Buffer contains 8.5g/l NaCl and 10g/l hydroxyethyl cellulose.

Lysis Buffer is 0.15M NH_4Cl^-, 10mM $KHCO_3$, 1mM EDTA

Whole Cell Binding Buffer is 50 mM HEPES, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.5% BSA, 0.01% NaN_3, adjusted to pH 7.2 with 1M NaOH.

Wash buffer is 50mM HEPES, 1mM $CaCl_2$, 5mM $MgCl_2$, 0.5% heat inactivated FCS, 0.5MNaCl adjusted to pH7.2 with 1M NaOH.

General molecular biology procedures can be followed from any of the methods described in "Molecular Cloning - A Laboratory Manual" Second Edition, Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory, 1989).

i) Cloning and expression of hMCP-1 receptor

The MCP-1 receptor B (CCR2B) cDNA was cloned by PCR from THP-1 cell RNA using suitable oligonucleotide primers based on the published MCP-1 receptor sequences (Charo *et al.*, 1994, *Proc. Natl. Acad. Sci. USA*, **91**, 2752). The resulting PCR products were cloned into vector PCR-II™ (InVitrogen, San Diego, CA.). Error free CCR2B cDNA was subcloned as a Hind III-Not I fragment into the eukaryotic expression vector pCDNA3 (InVitrogen) to generate pCDNA3/CC-CKR2A and pCDNA3/CCR2B respectively.

Linearised pCDNA3/CCR2B DNA was transfected into CHO-K1 cells by calcium phosphate precipitation (Wigler *et al.*, 1979, *Cell*, **16**, 777). Transfected cells were selected by the addition of Geneticin Sulphate (G418, Gibco BRL) at 1mg/ml, 24 hours after the cells had been transfected. Preparation of RNA and Northern blotting were carried out as described previously (Needham *et al.*, 1995, *Prot. Express. Purific.*, **6**, 134). CHO-K1 clone 7 (CHO-CCR2B) was identified as the highest MCP-1 receptor B expressor.

ii) Preparation of membrane fragments

[illegible] Membrane fragments were prepared using cell lysis/differential centrifugation method as described

previously (Siciliano *et al.*, 1990, *J. Biol. Chem.*, **265**, 19658). Protein concentration was estimated by BCA protein assay (Pierce, Rockford, Illinois) according to the manufacturer's instructions.

iii) Assay

^{125}I MCP-1 was prepared using Bolton and Hunter conjugation (Bolton *et al.*, 1973, *Biochem. J.*, **133**, 529; Amersham International plc]. Equilibrium binding assays were carried out using the method of Ernst *et al.*, 1994, *J. Immunol.*, **152**, 3541. Briefly, varying amounts of ^{125}I-labeled MCP-1 were added to 7µg of purified CHO-CCR2B cell membranes in 100 µl of Binding Buffer. After 1 hour incubation at room temperature the binding reaction mixtures were filtered and washed 5 times through a plate washer (Brandel MLR-96T Cell Harvester) using ice cold Binding Buffer. Filter mats (Brandel GF/B) were pre-soaked for 60 minutes in 0.3% polyethylenimine prior to use. Following filtration individual filters were separated into 3.5ml tubes (Sarstedt No. 55.484) and bound ^{125}I-labeled MCP-1 was determined (LKB 1277 Gammamaster). Cold competition studies were performed as above using 100 pM ^{125}I-labeled MCP-1 in the presence of varying concentrations of unlabelled MCP-1. Non-specific binding was determined by the inclusion of a 200-fold molar excess of unlabelled MCP-1 in the reaction.

Ligand binding studies with membrane fragments prepared from CHO-CCR2B cells showed that the CCR2B receptor was present at a concentration of 0.2 pmoles/mg of membrane protein and bound MCP-1 selectively and with high affinity (IC_{50} = 110 pM, K_d =120 pM). Binding to these membranes was completely reversible and reached equilibrium after 45 minutes at room temperature, and there was a linear relationship between MCP-1 binding and CHO-CCR2B cell membrane concentration when using MCP-1 at concentrations between 100 pM and 500 pM.

Test compounds dissolved in DMSO (5µl) were tested in competition with 100 pM labelled MCP-1 over a concentration range (0.01-50µM) in duplicate using eight point dose-response curves and IC_{50} concentrations were calculated.

Compounds tested of the present invention had IC$_{50}$ values of 50µM or less in

b) MCP-1 mediated calcium flux in THP-1 cells

The human monocytic cell line THP-1 was grown in a synthetic cell culture medium RPMI 1640 supplemented with 10 % foetal calf serum, 6mM glutamine and Penicillin-Streptomycin (at 50 µg streptomycin ml, Gibco BRL). THP-1 cells were washed in HBSS (lacking Ca^{2+} and Mg^{2+}) + 1 mg ml BSA and resuspended in the same buffer at a density of 3 x 10^6 cells/ml. The cells were then loaded with 1mM FURA-2/AM for 30 min at 37°C, washed twice in HBSS, and resuspended at 1x10^6 cells/ml. THP-1 cell suspension (0.9 ml) was added to a 5 ml disposable cuvette containing a magnetic stirrer bar and 2.1 ml of prewarmed (37°C) HBSS containing 1 mg ml BSA, 1 mM $MgCl_2$ and 2 mM $CaCl_2$. The cuvette was placed in a fluorescence spectrophotometer (Perkin Elmer, Norwalk, CT) and preincubated for 4 min at 37°C with stirring. Fluorescence was recorded over 70 sec and cells were stimulated by addition of hMCP-1 to the cuvette after 10 sec. $[Ca^{2+}]i$ was measured by excitation at 340 nm and 380 nm alternately and subsequent measurement of the intensity of the fluorescence emission at 510 nm. The ratio of the intensities of the emitted fluorescent light following excitation at 340 nm and 380 nm, (R), was calculated and displayed to give and estimate of cytoplasmic $[Ca^{2+}]$ according to the equation:-

$$[Ca^{2+}]i = K_d \frac{(R-Rmin)}{(Rmax-R)} (Sf2/Sb2)$$

where the K_d for FURA-2 Ca^{2+} complex at 37°C was taken to be 224nm. R_{max} is the maximal fluorescence ratio determined after addition of 10 mM Ionomycin, R_{min} is the minimal ratio determined by the subsequent addition of a Ca^{2+} free solution containing 5 mM EGTA, and Sf2/Sb2 is the ratio of fluorescence values at 380 nm excitation determined at R_{min} and R_{max}, respectively.

Stimulation of THP-1 cells with hMCP-1 induced a rapid, transient rise in $[Ca^{2+}]i$ in a specific and dose dependent manner. Dose response curves indicated an approximate EC_{50} of 2 nm. Test compounds dissolved in DMSO (10µl) were assayed for inhibition of calcium release by adding them to the cell suspension 10 sec prior to ligand addition and measuring the reduction in the transient rise in $[Ca^{2+}]i$. Test compounds were also checked for lack of agonist activity by addition in place of hMCP-1

[illegible] those [illegible] either directly [illegible]

colourimetric viability assay measuring the cleavage of a tetrazolium salt by the mitochondrial respiratory chain (Scudiero D.A. *et al.* 1988, *Cancer Res.*, **48**, 4827-4833).

Chemoattractants were introduced into a 96-well microtitre plate which forms the lower well of a chemotaxis chamber fitted with a PVP-free 5 µm poresize polycarbonate adhesive framed filter membrane (NeuroProbe MB series, Cabin John, MD 20818, USA) according to the manufacturer's instructions. The chemoattractant was diluted as appropriate in synthetic cell culture medium, RPMI 1640 (Gibco) or supplemented with 2 mM glutamine and 0.5% BSA, or alternatively with HBSS with Ca^{2+} and Mg^{2+} without Phenol Red (Gibco) plus 0.1% BSA. Each dilution was degassed under vacuum for 30 min and was placed (400 µl) in the lower wells of the chamber and THP-1 cells ($5x10^5$ in 100 µl RPMI 1640 + 0.5%BSA) were incubated in each well of the upper chamber. For the inhibition of chemotaxis the chemoattractant was kept at a constant submaximal concentration determined previously (1nM MCP-1) and added to the lower well together with the test compounds dissolved in DMSO (final DMSO concentration < 0.05% v/v) at varying concentrations. The chamber was incubated for 2 h at 37°C under 5 % CO_2. The medium was removed from the upper wells which were then washed out with 200 µl physiological saline before opening the chamber, wiping dry the membrane surface and centrifuging the 96-well plate at 600 g for 5 min to harvest the cells. Supernatant (150 µl) was aspirated and 10 µl of cell proliferation reagent, WST-1, {4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-phenyl disulfonate} plus an electron coupling reagent (Boehringer Mannheim, Cat.no. 1644 807) was added back to the wells. The plate was incubated at 37°C for 3 h and the absorbance of the soluble formazan product was read on a microtitre plate reader at 450 nm. The data was input into a spreadsheet, corrected for any random migration in the absence of chemoattractant and the average absorbance values, standard error of the mean, and significance tests were calculated. hMCP-1 induced concentration dependent cell migration with a characteristic biphasic response, maximal 0.5-1.0 nm.

In an alternative form of the above assay, fluorescently tagged cells can be used in order to assist in end point detection. In this case, the THP-1 cells used are fluorescently

[illegible]

for 4[illegible] minutes in the dark. Cells are harvested by centrifugation and resuspended in HBSS

(without Phenol Red) with Ca^{++}, Mg^{++} and 0.1% BSA. 50µl (2x105 cells) of the cell suspension are placed on the filter above each well and, as above, the unit is incubated at 37°C for 2 hours under 5% CO_2. At the end of the incubation, cells are washed off the upper face of the filter with phosphate buffered saline, the filter removed from the plate and the number of cells attracted to either the underside of the filter or the lower well estimated by reading fluorescence at 485nm excitation, 538nm emission wavelengths (fmax, Molecular Devices). The data was input into a spreadsheet, corrected for any random migration in the absence of chemoattractant and the average fluorescence values, standard error of the mean, percentage inhibition and IC_{50} of compounds under test and significance tests can be calculated. In addition to MCP-1 induced chemotaxis, this alternative form of the assay was also used to measure inhibition of RANTES (2nM) induced chemotaxis.

d) Binding to human peripheral blood mononuclear cells(PBMCs)

i) Preparation of human PBMCs

Fresh human blood (200ml) was obtained from volunteer donors, collected into sodium citrate anticoagulant to give a final concentration of 0.38%. The blood was mixed with Sedimentation Buffer and incubated at 37°C for 20 minutes. The supernatant was collected and centrifuged at 1700rpm for 5 minutes (Sorvall RT6000D). The pellet obtained was resuspended in 20 ml RPMI/BSA (1mg/ml) and 4 x 5mls of cells were carefully layered over 4 x 5mls of Lymphoprep® (Nycomed) in 15ml centrifuge tubes. Tubes were spun at 1700rpm for 30 minutes (Sorvall RT6000D) and the resultant layer of cells was removed and transferred to 50ml Falcon tubes. The cells were washed twice in Lysis Buffer to remove any remaining red blood cells followed by 2 washes in RPMI/BSA. Cells were resuspended in 5mls of Binding Buffer. Cell number was measured on a Coulter counter and additional binding buffer was added to give a final concentration of 1.25×10^7 PBMCs/ml.

ii) Assay

[^{125}I]MCP-1 was prepared using Bolton and Hunter conjugation (Bolton *et al*., 1973, *Biochem. J*., **133**, 529; Amersham International plc). Equilibrium binding assays were carried out using the method of Ernst *et al*., 1994, *J. Immunol*., **152**, 3543. Briefly, 50µl of ^{125}I-labeled

the assay. Total binding was determined in the absence of competing ligand. Non-specific

binding was defined by the addition of 5µl cold MCP-1 to give a final assay concentration of 100nM. Assay wells were made up to a final volume of 100µl with Whole Cell Binding Buffer and the plates sealed. Following incubation at 37°C for 60 minutes the binding reaction mixtures were filtered and washed for 10 seconds using ice cold Wash Buffer using a plate washer (Brandel MLR-96T Cell Harvester). Filter mats (Brandel GF/B) were pre-soaked for 60 minutes in 0.3% polyethylenimine plus 0.2% BSA prior to use. Following filtration individual filters were separated into 3.5ml tubes (Sarstedt No. 55.484) and bound ^{125}I-labeled MCP-1 was determined (LKB 1277 Gammamaster).

Test compound potency was determined by assay in duplicate using six point dose-response curves and IC_{50} concentrations were determined.

Compound No. 13 in Table I showed 94% inhibition at 20µm.

No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

Example 16

Pharmaceutical Compositions

The following Example illustrates, but is not intended to limit, pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg tablet
Compound X.	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w v paste)	2.25
Magnesium stearate	3.0

(b)

Tablet II	mg tablet
[illegible]	[illegible]
Maize starch	50.0

Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium	1.5

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	to adjust pH to 7.6
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f)

Injection II	(10 mg/ml)
Compound X	
Water for injection	to 100%

(g)

Injection III	(1mg ml, buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

(h)

Aerosol I	mg/ml
Compound X	10.0
Sorbitan trioleate	13.5
Trichlorofluoromethane	910.0
Dichlorodifluoromethane	490.0

(i)

Aerosol II	mg/ml
Compound X	0.2
Sorbitan trioleate	0.27
Trichlorofluoromethane	70.0
Dichlorodifluoromethane	280.0
Dichlorotetrafluoroethane	1094.0

(j)

Aerosol III	
Trichlorofluoromethane	

Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(k)

Aerosol IV	mg/ml
Compound X	2.5
Soya lecithin	2.7
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(l)

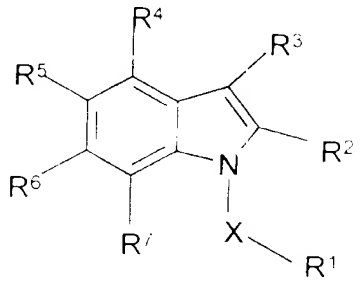
Ointment	ml
Compound X	40 mg
Ethanol	300 µl
Water	300 µl
1-Dodecylazacycloheptan-2-one	50 µl
Propylene glycol	to 1 ml

Note:

Compound X in the above formulation may comprise a compound illustrated in Examples. The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

Claims

1. A compound of formula (I)

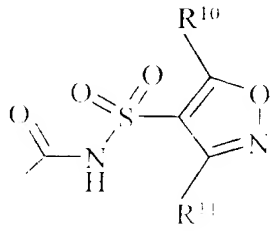


(I)

X is CH_2 or SO_2

R^1 is an optionally substituted aryl or heteroaryl ring;

R^2 is carboxy, cyano, $-C(O)CH_2OH$, $-CONHR^8$, $-SO_2NHR^9$, tetrazol-5-yl, SO_3H, or a group of formula (VI)



(VI)

where R^8 is selected from hydrogen, alkyl, aryl, cyano, hydroxy, $-SO_2R^{13}$ where R^{13} is alkyl, aryl, heteroaryl, or haloalkyl, or R^8 is a group $-(CHR^{12})_r-COOH$ where r is an integer of 1-3 and each R^{12} group is independently selected from hydrogen or alkyl; R^9 is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally subtituted heteroaryl such as 5 or 6 membered heteroaryl groups, or a group COR^{14} where R^{14} is alkyl, aryl, heteroaryl or haloalkyl; R^{10} and R^{11} are independently selected from hydrogen or alkyl

R^3 is hydrogen, a functional group, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally [illegible]

optionally substituted alkoxy, optionally substituted aralkyl, optionally substituted aralkyloxy, optionally substituted cycloalkyl;

R^4 is a group $NHCOR^{15}$, $NHSO_2R^{15}$ or $OCONR^{16}R^{17}$ where R^{15} is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl and R^{16} and R^{17} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted aryl and optionally substituted heteroaryl, with the proviso that at least one of R^{16} or R^{17} is other than hydrogen, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring which optionally contains further heteroatoms; and

R^5, R^6 and R^7 are independently selected from hydrogen, a functional group or an optionally substituted hydrocarbyl groups or optionally substituted heterocyclic groups;

and further provided that when R^4 is a group $NHCOR^{15}$, R^{15} is substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl.

2. A compound according to claim 1 wherein a group R^{15}, R^{16} and R^{17} as they appear in the definition of R^4, is substituted by at least one functional group, or an aryl or heterocyclyl groups, either of which may themselves be substituted by one or more functional groups or further aryl or heterocyclyl groups.

3. A compound according to any one of the preceding claims wherein R^4 is a group $NHCOR^{15}$ or $NHSO_2R^{15}$ and R^{15} is a substituted alkyl group or an optionally subsituted hetercyclyl or optionally substituted phenyl group.

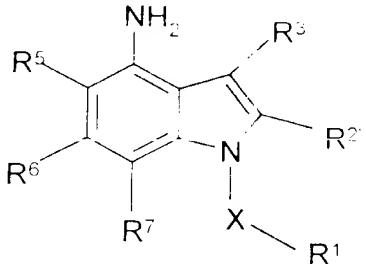
4. A compound according to claim 3 wherein R^{15} is alkyl substituted by a group of formula $NR^{19}R^{20}$ where R^{19} and R^{20} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{19} and R^{20} together form an optionally substituted ring which optionally contains further heteroatoms such as $S(O)_n$, oxygen and nitrogen, n is an integer of 1 or 2, m is 1 or 2

6. A compound according to any one of the preceding claims wherein R^1 is 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-chloro-4-fluorophenyl or 2,3-dichloropyrid-5-yl.

7. A compound according to any one of the preceding claims where X is CH_2.

8. A process for preparing a compound according to claim 1 which process comprises either

(a) where R^4 is $NHCOR^{15}$ or $NHSO_2R^{15}$, reacting a compound of formula (VII)



(VII)

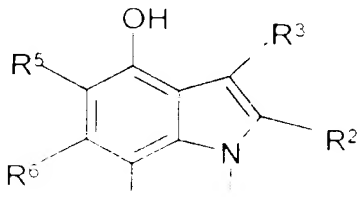
where X, R^1, R^3, R^5, R^6 and R^7 are as defined in claim 1, and R^2 is a group R^2 as defined in relation to formula (I) or a protected form thereof, with a compound of formula (VIII)

$$Z\text{-}R^{22}$$

(VIII)

where Z is a leaving group and R^{22} is a group COR^{15} or SO_2R^{15} where R^{15} is group R^{15} as defined in relation to formula (I) or a precursor thereof;

or (b) where R^4 is a group $OCONR^{16}R^{17}$, reacting a compound of formula (VIIA)



where X, $R^{2'}$, R1, R3, R5, R6 and R7 are as defined claim 1 and R^{2} is a group R^{2} as defined in claim 1 or a protected form thereof; with a compound of formula (VIIIA)

$$Z\text{-}CONR^{16}R^{17}$$

(VIIIA)

where Z, R16 and R17 are as defined above;

and thereafter if desired or necessary:

(i) converting a precursor group $R^{15'}$ to a group R15 and/or converting a group R15 to a different such group;

(ii) deprotecting a group $R^{2'}$ to a group R^{2}.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 in combination with a pharmaceutically acceptable carrier.

10. A compound according to any one of claims 1 to 7 for use in the preparation of a medicament for use in the treatment of disease mediated by monocyte chemoattractant protein-1 or RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted), such as inflammatory disease.